PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 1941,001WO1	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2005/012028	International filing date *(day/month/year)* 12 April 2005 (12.04.2005)	Priority date *(day/month/year)* 15 April 2004 (15.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SAMARITAN PHARMACEUTICALS, INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☒	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 October 2006 (19.10.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Yolaine Cussac e-mail: pt11@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

17/11

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/012028	12.04.2005	15.04.2004

International Patent Classification (IPC) or both national classification and IPC
A61K31/495, A61P25/28, C07D295/18

Applicant
SAMARITAN PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Kollmannsberger, M Telephone No. +49 89 2399-7364

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/012028

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-24,26; 25(part)

because:

☒ the said international application, or the said claims Nos. 1-24,26 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 25(part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24,26,27
	No:	Claims	25
Inventive step (IS)	Yes:	Claims	1-24,26,27
	No:	Claims	25
Industrial applicability (IA)	Yes:	Claims	25
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III-1. Claim 25 is directed to composition comprising compounds (I) together with a pharmaceutically acceptable carrier. Many such compositions are known. The initial phase of the search revealed a thus very large number of documents relevant to the issue of novelty of claim 25. So many documents were retrieved that it is impossible to determine which parts of this claim may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claim 25. The search with regard to claim 25 is only complete for the example compound mentioned in the description. Some illustrative documents have been cited for the other parts of claim 25.

III-2. Claims 1-24 and 26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the Art:

The following documents have been cited:

D1: WO 2004/108666 A (SAMARITAN PHARMACEUTICALS; GEORGETOWN UNIVERSITY; LECANU, LAURENT; GRE) 16 December 2004 (2004-12-16)

D2: LECANU L ET AL: "Identification, design, synthesis, and pharmacological activity of (4-ethyl-piperazin-1-yl)-phenylmethanone derivatives with neuroprotective

properties against beta-amyloid-induced toxicity" NEUROPHARMACOLOGY, PERGAMON PRESS, OXFORD, GB, vol. 49, no. 1, July 2005 (2005-07), pages 86-96, XP004963513 ISSN: 0028-3908

D3: WO 2004/035556 A (GLAXO GROUP LIMITED; ANCLIFF, RACHAEL; ELDRED, COLIN, DAVID; FOGDEN, Y) 29 April 2004 (2004-04-29)

D4: US-A-5 693 804 (DEBERNARDIS ET AL) 2 December 1997 (1997-12-02)

D5: WO 01/07435 A (MERCK PATENT GMBH; BOETTCHER, HENNING; GREINER, HARTMUT; HARTING, JUER) 1 February 2001 (2001-02-01)

D6: US 2004/034019 A1 (TOMLINSON RONALD ET AL) 19 February 2004 (2004-02-19)

D7: DE 23 04 155 A1 (ICHTHYOL-GESELLSCHAFT CORDES, HERMANNI & CO, 2000 HAMBURG) 1 August 1974 (1974-08-01)

D8: YUNG D K ET AL: "POTENTIAL ANTI ARRHYTHMIC AGENTS SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SOME PIPERAZINE AND ETHYLENEDIAMINE ANALOGS OF PROCAINAMIDE 1 N PROPYL-4-BENZOYL PIPERAZINE HYDRO CHLORIDE 1 N BUTYL-4-BENZOYL PIPERAZINE HYDRO CHLORIDE 1 N PROPYL-4-P-METHOXYBENZOYL PIPERAZINE HYDRO CHLORIDE 1 N PROPYL-4-P" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 57, no. 12, 1968, pages 2073-2080, XP009055767 ISSN: 0022-3549

D9: FUKUSHI H ET AL: "SYNTHESIS AND PLATELET-ACTIVATING FACTOR (PAF)-ANTAGONISTIC ACTIVITIES OF 1,4-DISUBSTITUTED PIPERAZINE DERIVATIVES" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 42, no. 3, March 1994 (1994-03), pages 541-550, XP001118308 ISSN: 0009-2363

D10: YOUNES-EL-HAGE S ET AL: "SYNTHESE ET ETUDE DE L'ACTIVITE ANTIDEPRESSIVE D'ARYL ET HETEROARYL CARBOXAMIDES DE LA BENZYLPIPERAZINE SYNTHESIS AND ANTIDEPRESSIVE ACTIVITY STUDY OF ARYL AND HETEROARYL CARBOXAMIDES OF BENZYLPIPERAZINE" ANNALES PHARMACEUTIQUES FRANCAISES, MASSON, PARIS, FR, vol. 58, no. 4, 2000, pages 254-259, XP008031993 ISSN: 0003-4509

D11: YOUNES S ET AL: "Synthesis and structure-activity relationships of novel arylalkyl 4-benzyl piperazine derivatives as sigma site selective ligands" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS

SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 35, no. 1, January 2000 (2000-01), pages 107-121, XP004350211 ISSN: 0223-5234

D12: BAZIARD-MOUYSSET G ET AL: "Synthesis and structure-activity relationships of novel 2-amino alkyl chromones and related derivatives as sigma site-selective ligands" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 33, no. 5, June 1998 (1998-06), pages 339-347, XP004127366 ISSN: 0223-5234

D13: CARCELLER E ET AL: "(PYRIDYLCYANOMETHYL)PIPERAZINES AS ORALLY ACTIVE PAF ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 35, no. 22, 1992, pages 4118-4134, XP002044180 ISSN: 0022-2623

D1-D3 are P-documents and will be disregarded in the PCT-procedure.

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise.

V-2. Novelty (Art. 33(2) PCT):

Although no complete search could be carried out for claim 25 it is nevertheless clear that claim 25 does not define novel subject-matter since D7-D13 disclose compositions included in its scope.

Claims 1-24, 26 and 27 are novel over D7-D13 because D7-D13 do not mention the use of the disclosed compounds for threating Alzheimer or neuropathy.

Claims 1-24, 26 and 27 are novel over D4-D6 which deal with compounds useful in the treatment of Alzheimer's disease. The compounds of D4 and D6 differ in the substituent corresponding to CH2-X in the present claims. The compounds of D5 have a benzimidazole instead of the phenyl ring.

V-3. Inventive step (Art. 33(3) PCT):

Closest state of the art can be seen in D4 which deals with compounds that differ in the substituent corresponding to CH2-X in the present claims (i. a. by an additional carbonyl group). The problem to be solved would be to find other compounds which can be used to treat Alzheimer's disease. D7-D13 disclose unrelated uses. The compounds of D6 differ from the claims in the same substituent as D4 and D5 describes benzimidazoles. The skilled man would thus have no motivation to arrive at the present claims 1-24, 26 and 27 in order to find compounds useful for the claimed purposes.

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/108666	16.12.2004	20.05.2004	02.06.2003
WO2004/035556	29.04.2004	14.10.2003	16.10.2002

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Generaldirektion 1	Directorate General 1	Direction générale 1

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Date
22.09.06

Reference	Application No./Patent No.
	05776434.2 - 2101 PCT/US2005012028
Applicant/Proprietor: Samaritan Pharmaceuticals, Inc., et al	

Entry into the European phase before the European Patent Office

These notes describe the procedural steps required for entry into the European phase before the European Patent Office (EPO). You are advised to read them carefully: failure to take the necessary action in time can lead to your application being deemed withdrawn.

1. The above-mentioned international patent application has been given European application No. **05776434.2**.

2. Applicants **without** a residence or their principal place of business in an EPC contracting state may themselves initiate European processing of their international applications, provided they do so before expiry of the 31st month from the priority date (see also point 6 below).

   During the European phase before the EPO as designated or elected Office, however, such applicants must be represented by a professional representative (Arts. 133(2) and 134(1), (7) EPC).

   Procedural acts performed after expiry of the 31st month by a professional representative who acted during the international phase but is not authorised to act before the EPO have no legal effect and therefore lead to loss of rights.

   Please note that a professional representative authorised to act before the EPO and who acted for the applicant during the international phase does not automatically become the representative for the European phase. Applicants are therefore strongly advised to appoint in good time any representative they wish to initiate the European phase for them; otherwise, the EPO has to send all communications direct to the applicant.

3. Applicants **with** a residence or their principal place of business in an EPC contracting state are not obliged to appoint, for the European phase before the EPO as designated or elected Office, a professional representative authorised to act before the EPO.
   However, in view of the complexity of the procedure it is recommended that they do so.

4. Applicants and professional representatives are also strongly advised to initiate the European phase using EPO Form 1200 (available free of charge from the EPO). This however is not compulsory.

5. **To enter the European phase before the EPO**, the following acts must be performed.
(N.B.: Failure validly to do so will entail loss of rights or other adverse legal consequences.)

5.1 If the EPO is acting as **designated** or **elected** Office (Arts. 22(1)(3) and 39(1) PCT respectively), applicants must, within 31 months from the date of filing or (where applicable) the earliest priority date:

a) Supply a translation of the international application into an EPO official language, if the International Bureau did not publish the application in such a language (Art. 22(1) PCT and R. 107(1)(a) EPC).
If the translation is not filed in time, the international application is deemed withdrawn before the EPO (R. 108(1) EPC).
This loss of rights is deemed not to have occurred if the translation is then filed within a two-month grace period as from notification of an EPO communication, provided a surcharge is paid at the same time (R. 108(3) EPC).

b) Pay the national basic fee (EUR 170,00) and, where a supplementary European search report has to be drawn up, the search fee (EUR 720,00 ; R. 107(1)(c) and (e) EPC).

c) If the time limit under Article 79(2) EPC expires before the 31-month time limit, pay the designation fee (EUR 80,00) for each contracting state designated (R. 107(1)(d) EPC).

d) If the time limit under Article 94(2) EPC expires before the 31-month time limit, file the written request for examination **and** pay the examination fee (EUR 1490,00 ; R. 107(1)(f) EPC).

e) Pay the third-year renewal fee (EUR 400,00) if it falls due before expiry of the 31-month time limit (R. 107(1)(g) EPC).

If the fees under (b) to (d) above are not paid in time, or the written request for examination is not filed in time, the international application is deemed withdrawn before the EPO, or the contracting-state designation(s) in question is (are) deemed withdrawn (R. 108(1) and (2) EPC). However, the fees may still be validly paid within a two-month grace period as from notification of an EPO communication, provided the necessary surcharges are paid at the same time (R. 108(3) EPC). For the renewal fee under (e) above, the grace period is **six** months from the fee's due date (Art. 86(2) EPC).

For an overview of search and examination fees, see OJ EPO 11/2005, 577 and 03/2006.

5.2 If the application documents on which the European grant procedure is to be based comprise more then ten claims, a claims fee is payable within the 31-month time limit under Rule 107(1) EPC for the eleventh and each subsequent claim (R. 110(1) EPC). The fee can however still be paid within a one-month grace period as from notification of an EPO communication pointing out the failure to pay (R. 110(2) EPC).

6. If the applicant had a representative during the application's international phase, the present notes will be sent to the representative, asking him to inform the applicant accordingly.

All subsequent communications will be sent to the applicant, or - if the EPO is informed of his appointment in time - to the applicant's European representative.

7. For more details about time limits and procedural acts before the EPO as designated and elected Office, see the EPO brochure

   How to get a European patent
   Guide for applicants - Part 2
   PCT procedure before the EPO - "Euro-PCT"

   This brochure, the list of professional representatives before the EPO, Form 1200 and details of the latest fees are now all available on the Internet under

   http://www.european-patent-office.org

Receiving section